

## Care Step Pathway - Cardiotoxicity

### Nursing Assessment

#### Look:

- Does the patient look unwell?
- Fatigued?
- Diaphoretic?
- SOB or in respiratory distress?
- Is there leg edema?

#### Listen for new and worsening symptoms:

- Change in energy level?
- SOB or DOE?
- Leg edema?
- Palpitations?
- Changes in BP?
- Dizziness or syncope?
- What exacerbates or improves symptoms?
- Any new prescribed or OTC meds? Illicit substances?
- Any underlying cardiac disease (CAD, MI, or other)?
- Prior radiation therapy?

#### Recognize:

- Determine specific toxicity and related grade (if applicable)
- Other related symptoms: hypotension, syncope, chest pain, DOE, SOB, palpitations, edema, etc.
- Impact of symptoms on QOL performance status
- Changes in cardiac function: ECG changes (prolonged QTc), decreased LVEF, elevated cardiac enzymes (troponin, CK)
- Assess for other changes in oxygen saturation, BP, lung function

### Grading Toxicity

**Heart failure (left ventricular):** A disorder characterized by the inability of the heart to pump blood at an adequate volume to meet tissue metabolic requirements.

#### Grade 1 (Mild)

Asymptomatic with laboratory or cardiac imaging abnormalities

#### Grade 2 (Moderate)

Symptoms with mild to moderate activity or exertion

#### Grade 3 (Severe)

Severe with symptoms at rest or with minimal exertion (intervention needed)

#### Grade 4 (Potentially Life-Threatening)

Life-threatening consequences (urgent intervention required)

#### Grade 5 (Death)

**QTc interval prolongation:** A finding of a cardiac dysrhythmia characterized by an abnormally long corrected QT interval.

#### Grade 1 (Mild)

QTc 450–480 ms

#### Grade 2 (Moderate)

QTc 481–500 ms

#### Grade 3 (Severe)

QTc  $\geq$ 501 ms on at least 2 separate ECGs

#### Grade 4 (Potentially Life-Threatening)

QTc  $\geq$ 501 or  $>$ 60 ms change from baseline *and* torsade de pointes, polymorphic ventricular tachycardia, or signs or symptoms of serious arrhythmia

#### Grade 5 (Death)

## Management

### Overall Strategy:

- Review concomitant treatments that may affect heart function, particularly the QTc interval (e.g., fluoroquinolones, ondansetron, HIV antivirals)
- Full cardiac workup at baseline: ECG (for encorafenib), ECHO/MUGA (for any MEK-containing regimen), cardiac enzymes, CBC, CMP, BNP, C-reactive protein, CXR. Do not start MEKi therapy if QTc >500 ms
- Monitor patients who already have or who are at significant risk of developing QTc prolongation and correct hypokalemia/hypomagnesemia prior to and during encorafenib administration
- The safety of binimetinib has not been established in patients with LVEF <50% or below institutional LLN at baseline
- Repeat ECHO for MEK-containing regimen at 1 month and every 2–3 months while on treatment. If ECG performed (on encorafenib), repeat ECG at 14 days, monthly x3, and then every 2–3 months while on treatment, more frequently if on medications affecting QTc, or as needed if patient starts new agents that may prolong QT interval
- Prevention (no known strategies), but encourage healthy lifestyle
- Introduce concept of dose reduction or dose holding when educating patients prior to initiation of therapy
- Assess adherence with BP medications if patients are hypertensive
- Whenever binimetinib is held, reduce the dose of encorafenib to a maximum of 300 mg once daily until binimetinib is resumed

### Grade 1 (Mild)

- Anticipate cardiology referral if condition worsens
- MEK inhibitors (cobimetinib and trametinib) to be held for a LVEF value decreased >10% from baseline and below the institution's LLN
- Promote adequate hydration and medication adherence
- Advise patients to avoid alcohol intake or other psychoactive substances
- Encourage evaluation of lipid panel to assess cardiovascular risk
- Promote healthy lifestyle
  - o Smoking cessation, control of comorbidities, stress reduction, weight control, exercise

### Grade 2 (Moderate)

- Anticipate cardiology referral
- Trametinib to be discontinued for symptomatic congestive heart failure or a LVEF value decreased  $\geq 20\%$  from baseline and below the institution's LLN
- Binimetinib to be discontinued for a persistent LVEF value decrease >10% but <20% from baseline and below the institution's LLN or for persistent LVEF decrease. After 4-week binimetinib hold, evaluate LVEF q2 weeks. Resume at lower dose of binimetinib if LVEF is above the LLN AND the absolute decrease from baseline is  $\leq 10\%$  AND the patient is asymptomatic. If the LVEF does not recover within 4 weeks, permanently discontinue binimetinib
- Dabrafenib to be withheld for a LVEF value decreased >20% from baseline and below the institution's LLN
- For recurrent Grade 2 LVEF decrease (EF 40–50% or 10–19% drop from baseline), encorafenib to be withheld for up to 4 weeks; if improved to Grade 0/1 or pretreatment level, then the dosage may be resumed; if no improvement, encorafenib should be discontinued
- Anticipate prompt evaluation of current cardiac symptoms by oncologist or cardiologist if there are nonurgent cardiac symptoms
- Seek immediate care in emergency department for chest pain/pressure to evaluate for MI

### Grades 3-4 (Severe or Life-threatening)

- Anticipate urgent cardiology admission
- Assess cardiac function: lipid profile, ECG, ECHO/MUGA, stress test, BNP, cardiac enzymes
- For QTc >500 ms AND  $\leq 60$  ms increase from baseline, hold encorafenib or vemurafenib until QTc interval is  $\leq 500$  ms (after controlling for cardiac risk factors for QTc interval prolongation) Resume at lower dose. If QTc prolongation recurs, permanently discontinue encorafenib or vemurafenib
- For QTc >500 ms AND >60 ms increase from baseline, permanently discontinue encorafenib or vemurafenib
- For persistent LVEF decrease (i.e.,  $\geq 20\%$  drop from baseline and below the institution's LLN or any EF  $\leq 39\%$ ), all targeted therapies to be permanently discontinued
- Seek immediate care in emergency department for chest pain/pressure to evaluate for MI

BNP = brain natriuretic peptide; BP = blood pressure; CAD = coronary artery disease; CBC = complete blood count; CK = creatine kinase; CMP = complete metabolic panel; CXR = chest radiograph; DOE = dyspnea on exertion; ECG = electrocardiography; ECHO = echocardiography; EF = ejection fraction; GI = gastrointestinal; HIV = human immunodeficiency virus; LLN = lower limit of normal; LVEF = left ventricular ejection fraction; MI = myocardial infarction; MUGA = multigated acquisition scan; OTC = over the counter; QOL = quality of life; SOB = shortness of breath.